HISTOCHEMICAL STUDIES ON INTRAVENOUSLY ADMINISTERED FAT EMULSION : With special reference to differences in the metabolic process of various infused fatty substances

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HISTOCHEMICAL STUDIES ON INTRAVENOUSLY ADMINISTERED FAT EMULSION

With special reference to differences in the metabolic process of various infused fatty substances

by

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I. INTRODUCTION

Previously, ASADA of our laboratory had carried out histochemical studies on the metabolic process of fat when cod liver oil emulsion, which could be administered intravenously, was infused into animals. As a conclusion, he expounded that the infused fat globules were first phagocytized by the alveolar phagocytes, KUPFFER's stellate cells of the liver, reticuloendothelial cells of the spleen, and then changed from the status of neutral fat into phospholipid in these cells to enter through the blood stream into the hepatic parenchymatous cells where they were metabolized.

Subsequent to this study, OTANI of our laboratory enunciated that the intravenous administration of fat emulsion made out of material containing highly unsaturated fatty acids in large quantity, such as cod liver oil*, and containing lower fatty acids also, such as cocoanut oil, caused a remarkable hemolysis, while there was hardly any possibility of this danger in the case of an infusion of fat emulsion prepared from fatty substances like sesame oil containing higher fatty acids without highly unsaturated acid.

* OTANI first reasoned that the hemolysis and fatty liver, observed when cod liver oil emulsion was infused, were caused by the lower fatty acid in the emulsion. As a result of qualitative tests on fatty acid by using the chromatographic method, TAN of our laboratory later disclosed that the real cause of such phenomena was the highly unsaturated fatty acid contained in the cod liver oil.

On these empirical grounds, it goes without saying that in order to achieve the objective of parenteral nutrition with fat by its intravenous infusion in an emulsified form, as has been attempted by us, the fatty substance to be used should be not cod liver oil or the like but sesame oil or the like.

On the other hand, according to the recent studies by TAN, every higher fatty acid is absorbed through the thoracic duct, while a greater part of lower fatty acid is directly absorbed through the portal vein to be metabolized in the liver.

From the above facts, it may be supposed that the metabolic process of fat varies by the chain length or the degree of unsaturation of the fatty acids contained in the administered fat. The author histochemically examined the metabolic process of fat when sesame oil emulsion and triolein emulsion were infused into animals intravenously, and also when olive oil and butter fat were administered to them orally. The results thus obtaind have been compared with the previous reports by ASADA, in which he used cod liver oil emulsion. The author also attempted to elucidate how the metabolic process of fat varies by the quality of the fatty acids contained in these emulsions.

II. MATERIALS AND METHODS

1) Experimental Materials

Fat Emulsion : In the present experiment, 15 per cent sesame oil emulsion and 15 per cent emulsion of artificially synthetized triolein were employed. On the other hand, butter fat and olive oil were used in the experiment on the oral administration of fat. A standard dose of the intravenous administration of the fat emulsion was determined to be 3.3 cc of 15 per cent fat emulsion per kg body weight.

Experimental Animals : Adult cats representing carnivorous animals, and adult rabbits representing herbivorous animals were subjected to the experiment. They had been maintained on fixed diet at least for a week and were fasted for 24 hours prior to the experiment in order to bring them into a postabsorptive state.

2) Experimental Methods

The standard dose of the fat emulsion as above mentioned was administered intravenously. Then, after infusion, the animals were successively sacrificed by bleeding without anesthesia at definite intervals. In each time series, 2 or 3 animals were grouped together for the investigation. All tissues for sectioning were placed at once in 10 per cent neutral formol solution or in BAKER's solution. Conforming to the method as previously employed by ASADA, carbowax-embedding was mainly used, but the freezing method was employed if deemed necessary. Further, the thickness of the sections was defined as 12 μ in the lung and 6 μ in the liver and spleen.

The sections were stained for fat by GOLDMANN's Sudan III method (ASADA's modification) and by the Oil red O staining method, and for phospholipid by SMITH-DIETRICH's and BAKER's methods. When needed hematoxilin-eosin method was also employed.

III. RESULTS

I) Intravenous Administration of the Fat Emulsion

A. Infusion into Cats

i) Intravenous Administration of the Sesame Oil Emulsion.

After the adult cats, ranging in weight from 2.0 to 3.0 kg, received an intravenous administration of the standard dose of the sesame oil emulsion, they were sacrificed at definite intervals. In this way, the author examined histochemically the metabolic process of the infused fat (Table 1).

Table 1 Changes of Fat Content in Various Organs Following Intravenous Administration of Sesame Oil Emulsion into Cats

Time after infusion	Lung	Liver		Spleen
		Stellate cells	Liver cells	
10 min.	⧺	⧺	−	⧺
30 min.	⧺	⧺	±	⧺
1 hr.	+	+	±	+
2 hrs.	+	±	±	±
3 hrs.	±	±	+	±
4 hrs.	±	±	±	±
6 hrs.	−	−	±	−
24 hrs.	−	−	−	−
Control	−	−	−	−

At the earliest interval after infusion, the fine fat globules were still recognizable within the vessels in all organs. After 30 minutes, however, there was no evidence of fat globules in the blood. This fact seems to indicate that the infused fat is disposed of in certain organs within 30 minutes after infusion.

Lung: The infused fat globules were already phagocytized by numerous so-called "alveolar phagocytes" at 10 to 30 minute intervals after infusion (Fig. 1). However, the number of these cells phagocytizing the fat globules was somewhat less than the case of the cod liver oil emulsion as reported by ASADA. Most of these fat-filled phagocytes existed on the interalveolar walls, but some of them were observed to be separated from the alveolar walls into the alveolar spaces. One hour after infusion, the alveolar phagocytes containing the fat globules considerably decreased in number. A very small number of these cells were still found 4 hours after infusion, but thereafter the alveolar phagocytes contained no fat.

The phagocytized fat globules of grosser size were found to fill up the cytoplasma of the hypertrophied alveolar phagocytes in the 10 and 30 minute cases, produced a reddish yellow colour by the Sudan stain, and indicated a positive reaction for the SMITH-DIETRICH and BAKER stains (Fig. 2 and 3). Thereafter, as time went on, the fat granules in these cells gradually intensified their yellowish tone with Sudan and showed a stronger positive reaction for the lipoid test. These results suggest that the infused fat globules start to change into phospholipid from

the neutral fat immediately after infusion in the alveolar phagocytes, and gradually disappear from the same by being released into the blood stream.

Liver: In the liver, the fat globules were chiefly phagocytized by the KUPFFER stellate cells. In the 10 minute cases, the infused fat globules were already phagocytized by numerous KUPFFER cells, especially at the peripheries of the hepatic lobules; thus the stellate cells were hypertrophied and the nuclei were pushed aside in the corner of these cells. However, the number of the KUPFFER cells containing the infused fat was far less than that of the alveolar phagocytes previously mentioned. These stellate cells gradually decreased in number with the passage of time and almost disappeared in the 4 hour cases. A greater part of the infused neutral fat was histochemically confirmed to change gradually into phospholipid in the stellate cells like in the alveolar phagocytes.

On the other hand, there was no evidence that the infused fat globules infiltrated directly into the parenchymatous cells in the form of neutral fat. In the 30 minute or more post-infusion cases, however, phospholipid was found in small quantity within the parenchymatous cells, especially those in the peripheries of the hepatic lobules, in the fine granular form. Increasing gradually, this could be observed diffusely in the peripheries of the hepatic lobules in the 3 hour cases (Fig. 4). The amount of this phospholipid, however, was far less than the case of the cod liver oil emulsion (Fig. 5). Thereafter, the above phospholipid gradually decreased and almost entirely disappeared in the 24 hour cases.

In addition, there was no difference between the findings in the right hepatic lobes and those in the left.

Spleen: In the 10 or 30 minute cases, the region of the red pulp, especially the marginal zone of the white pulp and ellipsoids, was heavily infiltrated with the infused fat globules, a part of which appeared to deposite outside of the cells, but the majority were phagocytized within the reticular cells in the splenic red pulp, the so-called splenocytes and the endothelial cells of the splenic sinuses. In the one hour cases, the fat-filled reticuloendothelial cells slightly decreased in number but were to be observed all through the red pulp, and hardly any isolated fat globules outside of the cells were recognized. These cells gradually decreased subsequently and almost entirely disappeared in the 4 hour cases. It was evidenced that the change of the infused neutral fat into phospholipid proceeded in the above mentioned cells in the same manner as was observed in the lung and liver.

On the other hand, the same phospholipid as observed in the hepatic parenchymatous cells was found, though to a slighter degree, in a part of the splenic cords of the red pulp; the quantitative change of which in the process of time coincided with that in the liver.

Fat Embolism, etc.: There was no evidence of fat embolism, hyperemia or any other pathologic changes in all organs. Since the fat globules could not be discovered in any cell in the kidney nor in the epitheliums of the interlobular bile ducts, it would not be very extravagant to believe that practically no fat was excreted by these routes.

In summary of the findings described above, the infused fat globules were phagocytized by the alveolar phagocytes, KUPFFER's cells of the liver, reticuloendothelial cells of the spleen shortly after infusion, then the neutral fat gradually changed into phospholipid in these cells and disappeared again therefrom. At the same time, phospholipid was recognized in the hepatic parenchymatous cells almost concurrently. Namely, in conformity with the results reported by ASADA, this demonstrates that the phospholipid, which had been produced in the reticuloendothelial cells from the infused fat globules phagocytized thereby, was released into the blood stream and passed on to the hepatic parenchymatous cells secondarily. However, comparing the amount of this phospholipid in the case of the sesame oil emulsion as against that of the case of the cod liver oil emulsion, the former was far less than the latter (Table 6).

Further review of the qualitative composition of these emulsions discloses that the cod liver oil emulsion contains glycerinesters of highly unsaturated fatty acids in relatively large quantity, while the sesame oil emulsion does not have any trace of highly unsaturated fatty acid. Hence, it is thought that the amount of the phospholipid appearing in the hepatic parenchymatous cells was vitally affected by the existence of highly unsaturated fatty acids in the infused fat emulsion. Furthermore, since the amount of the infused fat was always standardized, it is justifiable to assume that the phospholipid, produced from the glycerinesters of highly unsaturated fatty acids contained in the infused fat emulsion, proceeds in whole into the hepatic parenchymatous cells, while some of the phospholipid produced from the glycerinesters of higher fatty acids without highly unsaturated acid, enters directly into the hepatic parenchymatous cells, but the other part goes into the extrahepatic tissues in parallel with the former movement.

ii) Intravenous Administration of the Triolein Emulsion

The standard dose of the triolein emulsion was infused intravenously, and the same experiments were repeated. The results are as follows (Table 2): The infused

Table 2 Changes of Fat Content in Various Organs Following Intravenous Administration of Triolein Emulsion into Cats

Time after infusion	Lung	Liver		Spleen
		Stellate cells	Liver cells	
10 min.	++	++	−	+
30 min.	++	++	±	+
1 hr.	+	+	±	+
3 hrs.	±	±	±	±
6 hrs.	−	−	−	−
Control	−	−	−	−

fat globules were found in the blood stream until 30 minutes after infusion.

Lung: The infused fat globules were already phagocytized by numerous alveolar phagocytes, but the number of these cells was somewhat less than the ones observed in the case of the sesame oil emulsion (Fig. 6).

Liver: The number of the stellate cells phagocytizing the fat globules was comparable to the case of the sesame oil emulsion, but these cells were not so hypertrophied.

A small amount of phospholipid was barely recognizable in fine granular form in the peripheries of the hepatic lobules only at the intervals of from 30 minutes to 3 hours after infusion (Fig. 7).

Spleen: In the spleen, the reticuloendothelial cells phagocytizing the infused fat globules were also somewhat fewer than those in the case of the sesame oil emulsion.

In addition, the neutral fat was changed into phospholipid in the alveolar phagocytes, stellate cells of the liver, reticuloendothelial cells of the spleen, like the case of the infusion of the sesame oil emulsion.

In summary of the findings above mentioned, the phospholipid, changed from the infused neutral fat in the reticuloendothelial cells of the lung, liver and spleen, entered into the hepatic parenchymatous cells through the blood stream, but its amount was less than that in the sesame oil emulsion case.

The sesame oil emulsion contains glycerinesters not only of saturated higher fatty acids such as myristic acid, palmitic acid and stearic acid but also unsaturated higher fatty acids such as oleic acid and linoleic acid. In contrast, the triolein emulsion contains only glycerinester of oleic acid. Accordingly, judging from the difference in the amount of the phospholipids observed in the hepatic parenchymatous cells when the cod liver oil, sesame oil and triolein emulsions were intravenously infused, oleic acid, although classified as an unsaturated fatty acid, is understood to be shifted into the extrahepatic tissues as phospholipid and disposed of there in larger quantity than saturated higher fatty acid. In remarkable contrast, it is understood that highly unsaturated acid is exclusively shifted into the hepatic parenchymatous cells as phospholipid and disposed of therein. Recently, HIROSE demonstrated that the degree in which the fat deposited in the liver was slighter in the case of the oral administration of oleic acid than the result obtained with palmitic acid. The results cited above are well in accord with the ones obtained by us.

As previously mentioned, the amount of the fat phagocytized by the reticuloendothelial cells of various organs, when the cod liver oil, sesame oil and triolein emulsions were intravenously infused, was the highest in the case of the cod liver oil emulsion, the next being the case of the sesame oil emulsion, and the lowest was that of the triolein emulsion. Moreover, the fat was always infused in the same, definite quantity. Accordingly, it is conceived that a part of glycerinester of saturated higher fatty acid and that of unsaturated higher fatty acid such as oleic acid, linoleic acid is transported directly to fat depots, as claimed by SCHOENHEIMER et al..

B. Infusion into Rabbits

i) Intravenous Administration of the Sesame Oil Emulsion

After intravenous administration of the standard dose of the sesame oil emulsion into rabbits, each weighing approximately 2.0 kg, they were sacrificed at definite

intervals (Table 3).

Table 3 Changes of Fat Content in Various Organs Following Intravenous Administration of Sesame Oil Emulsion into Rabbits

Time after infusion	Lung	Liver		Spleen
		Stellate cells	Liver cells	
10 min.	+	++	−	++
20 min.	+	++	−	++
30 min.	+	++	−	++
45 min.	+	++	−	++
1 hr.	+	++	±	++
2 hrs.	+	+	±	+
3 hrs.	+	+	+	+
4 hrs.	±	+	±	+
6 hrs.	±	±	±	±
12 hrs.	−	+	±	+
24 hrs.	−	−	−	±
48 hrs.	−	−	−	−
Control	−	−	−	−

The infused fat globules were still observable in the blood stream in the 30 minute cases, but thereafter these globules were entirely absent from the blood stream.

Lung : The infused fat globules started to be phagocytized by the alveolar phagocytes shortly after infusion, but these cells were very few in number as compared with those of the cat. The observed changes of the infused neutral fat into phospholipid in these cells were very slight in degree.

Liver : The infused fat globules were remarkably phagocytized by the KUPFFER stellate cells. In the 20 and 30 minute cases, the stellate cells, especially in the peripheries of the hepatic lobules, phagocytized the fat globules and hypertrophied (Fig. 8). The finding that the neutral fat changed into phospholipid in these stellate cells was very weak too.

Direct infiltration of the infused fat globules into the parenchymatous cells was not found. But in the one hour cases, phospholipid was found to appear slightly in the parenchymatous cells in the fine granular form. The amount reached its maximum 3 hours after infusion, then again diminished gradually and almost disappeared in the 12 hour cases. As compared with the findings of ASADA, the present findings indicated a far slighter appearance of the phospholipid in the parenchymatous cells both in the quantity and in the length of time.

Spleen : The infused fat globules were phagocytized by the reticuloendothelial cells in the red pulp, especially in the marginal zone of the splenic nodules. The number of these cells was very great up to one hour after infusion. The neutral fat was changed into phospholipid just as in the stellate cells.

Summarizing the above findings, it is postulated that the rabbit is weaker in the ability to dispose of fat than the cat, and that the lung of the rabbit is

weaker in fat disposal than that of the cat, so that the rabbit utilizes the liver and spleen, instead of the lung, to dispose of fat. Namely, the opinion asserted by ASADA was also confirmed in the case of the infusion of the sesame oil emulsion, a vegetable fat, into the rabbit, a herbivorous animal. On the other hand, it was observed that the amount of the phospholipid appearing in the hepatic parenchymatous cells had the same tendency as in the case of cats.

ii) Simultaneous Infusion of Methionine with the Sesame Oil Emulsion

Recently, the lipotropic action of methionine has come everybody's attention. ASADA and others previously clarified the fact that methionine accelerated phagocytosis and lipoidization of fat by the reticuloendothelial cells, and secondarily expediated fatty acid oxidation in the hepatic parenchymatous cells. In order to histochemically reexamine such effects of methionine, the author has intravenously infused the sesame oil emulsion with 5 mg of *l*-methionine per kg body weight into rabbits (Table 4).

Table 4 Changes of Fat Content in Various Organs Following Administration of *l*-Methionine (5 mg/kg) with Sesame Oil Emulsion into Rabbits

Time after infusion	Lung	Liver		Spleen
		Stellate cells	Liver cells	
10 min.	+	++	−	++
30 min.	+	###	±	###
1 hr.	+	###	+	++
2 hrs.	+	++	±	++
4 hrs.	±	+	±	+
6 hrs.	−	±	−	+
Control	−	−	−	−

There was not very great difference on the state of phagocytosis of the infused fat globules by the alveolar phagocytes, stellate cells and reticuloendothelial cells of the spleen between the present case and the case of the single infusion of the sesame oil emulsion. However, remarkably activated lipoidization was observed in these cells, and a greater part of the infused fat was already changed into phospholipid at the 10 and 30 minute intervals after infusion (Fig. 9).

In addition, the lapse of time in which the fat disappeared from these cells was somewhat shorter than the case of the single infusion.

In the hepatic parenchymatous cells, phospholipid was already found, though to a slight degree, 30 minutes after infusion, and had already disappeared after 6 hours.

Notwithstanding the fact that the phospholipid was being produced in the reticuloendothelial cells of the rabbit as actively as in the cat, the amount of the phospholipid appearing in the hepatic parenchymatous cells was even less than the case of the single infusion of the sesame oil emulsion. This fact supports the ARTOM and HASHINO opinion that methionine accelerates not only the lipoidization of neutral fat in the reticuloendothelial cells but also the oxidation of phospholipid.

iii) Intravenous Administration of the Sesame Oil Emulsion into Starved Rabbits

At the onset of the experiments mentioned previously, all the animals were fasted for 24 hours in order to avoid the influences of alimentary fat and mobilized depot fat due to starvation. This precaution was taken on the basis of ASADA's empirical findings that appearance of fat in each organ was held to the minimum at this "postabsorptive state". But in practice, patients with malnutrition due to the limitation of oral dining are the objects of our clinical application of this fat emulsion. It is assumed that the energy of these patients would be supplied by the mobilization of depot fat, and then lipids in large quantity would be disposed in the liver. Therefore, it was necessary to examine the metabolic process of fat in the liver when the fat emulsion was infused intravenously in such a situation.

Since we could not distinguish the infused fat from the hunger fat in cases of too long a starvation, the 48 hour intervals after diet, at which the hunger fat was only slightly mobilized, were selected for the experiments under starvation status. The standard dose of the sesame oil emulsion was infused intravenously into the starved rabbits.

In these cases, phospholipid appeared in the hepatic parenchymatous cells in far greater quantities than the case of the infusion into the normal animals in every case from one hour to 6 hours after infusion; diffused phospholipid was observed to be remarkable in the peripheries of the hepatic lobules (Fig. 10). This suggests that intravenous administration of this fat emulsion into the starved animals would cause a considerable overload on the liver.

HASHINO of our laboratory emphasized that in case of infusion into starved animals, a larger quantity of glucose and various vitamins should be infused simultaneously in addition to the fat emulsion. According to this opinion, 5mg of methionine, 2mg of riboflavin, 10 mg of *l*-ascorbic acid, 4mg of niacin amide, 5mg of pantothenic acid, 2mg of thiamin and 3.3cc of 20 per cent glucose solution per kg body weight were administered intravenously into the starved rabbits as previously mentioned with the standard dose of the sesame oil emulsion. In this case, the amount of the phospholipid appearing in the hepatic parenchymatous cells was only observed to an extremely slight degree (Fig. 11). This histochemical finding suggests the fact that in case of the intravenous administration of sesame oil emulsion into starved animals, the addition of glucose and the above mentioned drugs to the fat emulsion is not only useful but also necessary.

iv) Repeated Infusion of the Sesame Oil Emulsion on Consecutive Days

ASADA reported as follows: When repeated infusion of the cod liver oil emulsion was made for long date at a rate of 0.25g of fat per kg body weight per day into rabbits, lipids would accumulate in various organs and eventually might develop a fatty liver. The author investigated to see if the above malignant effect would be inflicted on the liver by the repeated infusion of the sesame oil emulsion.

Namely, after repeated daily intravenous administrations of the standard dose of the sesame oil emulsion into rabbits, they were sacrificed at definite date (Table

5).

Table 5 Changes of Fat Content in Various Organs Following a Repeated Infusion of Sesame Oil Emulsion into Rabbits

	Days of infusion	Days after latest infusion	Lung	Liver		Spleen
				Stellate cells	Liver cells	
Single Infusion of Sesame Oil Emulsion	7	1	−	±	−	+
	10	1	−	±	−	+
	14	1	−	+	−	++
	17	1	−	+	−	++
	21	1	±	++	−	++
	35	1	+	+++	−	+++
	49	1	+	+++	−	+++
	21	3	−	+	−	++
	21	5	−	+	−	++
	21	7	−	±	−	++
	21	14	−	±	−	+
	21	28	−	−	−	±
Fat Emulsion + Methionine & Riboflavin	21	1	−	+	−	++
	49	1	±	++	−	++
Control			−	−	−	−

Lung : The fat-filled alveolar phagocytes were scarcely recognized till the case of 21 consecutive infusions. Thereafter, however, these cells were slightly observed in hypertrophied status as the number of infusions were further increased.

Liver : In the KUPFFER stellate cells, no fat was found up to 7 or 10 days, but with further repeated infusion, the stellate cells phagocytizing the fat increased in number. The fat in these stellate cells was metabolized in the same and disappeared within one or two weeks when the infusion was interrupted after 21 day's consecutive application.

On the other hand, the phospholipid in the hepatic parenchymatous cells was scarcely observed even in the 49 day cases (Fig. 12). Of course, there was no evidence of the development of a fatty liver (Fig. 13). The present findings are worthy of our attention as compared with the results obtained by the use of the cod liver oil emulsion.

Spleen : The more frequently the infusion was carried out, the more remarkably was the phagocytosis of the fat by the reticuloendothelial cells. This was observed particularly in the reticular cells not only in the red pulp but also even in the white pulp. These fat-charged cells were gradually decreased when the infusion had been stopped after the 21st infusion. Compared with the case of the stellate cells, longer time was needed for the fat to disappear from these cells, and even 4 weeks after interruption of the infusion, these cells were still existent although not very many.

Comparing the present results as against the reports of ASADA, it was clearly demonstrated that the fat deposited more slightly in each organ and the disposition of the fat in the body was more smoothly and rapidly carried out in the former than the latter.

From the results obtained in the present starving experiments and the previous reports from our laboratory, it is thought that when glucose and various vitamins are infused simultaneously with the fat emulsion, the repeatedly infused fat will be metabolized and utilized more smoothly. In fact, when 5mg of methionine, 2mg of riboflavin and 3.3cc of 5 per cent glucose per kg body weight were repeatedly infused together with the sesame oil emulsion, the accumulation of lipids was very slight as compared with the case of the repeated single infusion (Table 5). Moreover, HAYASHI of our laboratory observed the fact that lipids were scarcely deposited in each organ, when the sesame oil emulsion was infused repeatedly into the normal rabbits for 8 months together with riboflavin and *l*-ascorbic acid.

In addition, no foreign body giant cells, cell infiltration or any other pathologic changes were observed in all the rabbits after repeated infusion.

Ⅱ) Oral Administration of Various Kinds of Oil

Butter fat, which contains glycerinesters of lower fatty acids in relatively large quantity and contains no glycerinester of highly unsaturated acid, and olive oil, which consists of glycerinesters of higher fatty acids without highly unsaturated acid, and the sesame oil emulsion, were given respectively at a rate of 15g of fat per kg body weight to the cats through a catheter introduced into the stomach, and then they were sacrificed at 6 hours thereafter when the fat was supposed to be most vigorously absorbed.

Comparing the findings in the case of the oral administration of butter fat as against olive oil, the former was somewhat more vigorous in the phagocytosis of fat by the alveolar phagocytes, stellate cells and reticuloendothelial cells of the spleen than the latter.

There was also a remarkable difference between the amount of the phospholipids appearing in the hepatic parenchymatous cells in the cases of butter fat and olive oil. In the case of butter fat, phospholipid was found diffusely in the peripheries of the hepatic lobules in large quantity (Fig. 14), but in the cases of olive oil and sesame oil emulsion, phospholipids were observed only in an extremely small quantity (Fig. 15). Like the results obtained in the experiments on the intravenous administration of the fat emulsion, it was observed that the phospholipids, produced from glycerinesters of saturated higher fatty acids as well as oleic acid and linoleic acid by the oral administration of fat, entered not only into the hepatic parenchymatous cells but also into the extrahepatic tissues to be metabolized, whereas the phospholipids, produced from glycerinesters of lower fatty acids, entered only into the hepatic parenchymatous cells to be disposed.

IV. DISCUSSION

Up to recent years, there was unanimous agreement that the liver is the prin-

cipal site for the oxidation of fatty acid, and that every fatty acid is further oxidized in the extrahepatic tissues only after it is broken down to ketone bodies in the liver. Since LEHNINGER, however, demonstrated "in vitro" that the heart muscle was able to oxidized fatty acid directly, the ability in fatty acid oxidation of various extrahepatic tissues has invited general attention and come to be the subject of hot debate. GEYER et al. reported that although the liver functions chiefly to break down fatty acid into acetoacetate, the extrahepatic tissues function to oxidize fatty acid completely. KENNEDY and LEHNINGER, moreover, believed that short chain even carbon fatty acid forms chiefly acetoacetic acid in the liver, while long chain even carbon fatty acid yields chiefly carbon dioxide under identical conditions. Accordingly, the general tendency has been gradually changed to assume that the process of fatty acid oxidation is divided into direct oxidation, in which fatty acid is completely oxidized in the liver and extrahepatic tissues, and indirect oxidation, in which the same is finally oxidized in the extrahepatic tissues after conversion into ketone bodies in the liver.

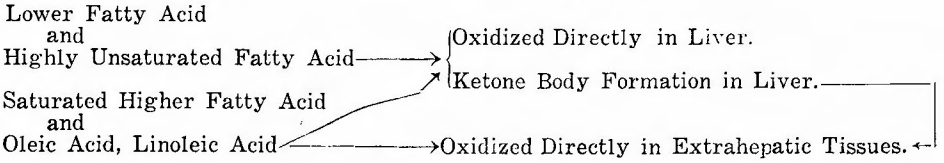
The author attempted comparative study of such findings obtained in the case of the intravenous infusion of various fat emulsions, prepared respectively from different kinds of fat, into the animals, and also in the case of the oral administration of various kinds of oil. The above ways and means led the author to believe he had succeeded in clarifying the conclusion that the phospholipids, produced from glycerinesters of saturated higher fatty acids such as stearic acid, palmitic acid and myristic acid, as well as the same from glycerinesters of unsaturated higher fatty acids such as oleic acid and linoleic acid, would enter into the hepatic parenchymatous cells in small percentage only, while the phospholipids produced from glycerinesters of lower fatty acids or glycerinesters of highly unsaturated acids would enter into the hepatic parenchymatous cells almost in the whole or at least in a very large quantity to be disposed there (Table 6).

Table 6 Phospholipid Content in Hepatic Parenchymatous Cells Following Intravenous Administration of Various Fat Emulsions into Cats

Remarks	10 min.	30 min.	1 hr.	3 hrs.	6 hrs.	24 hrs.
Cod Liver Oil Emulsion (ASADA)	−	−	+	++	+	±
Sesame Oil Emulsion	−	±	±	+	±	−
Triolein Emulsion	−	±	±	±	−	

From the above facts, it is thought that lower fatty acid or highly unsaturated acid enters into the hepatic parenchymatous cells, in which major part of the same is broken down to ketone bodies and thereafter carried through the blood stream to the every tissue of the body to be oxidized, whereas the major part of saturated fatty acid or oleic acid, linoleic acid is directly decomposed and metabolized to the final stage of water and carbon dioxide in the liver and extrahepatic tissues, and only a part of them undergoes indirect oxidation after being changed into ketone bodies in the hepatic parenchymatous cells (Fig. 16).

Fig. 16



In fact, repeated infusion of the cod liver oil emulsion, of which the phospholipid produced was disposed in the liver in large quantity, caused a remarkable accumulation of the phospholipid in the hepatic parenchymatous cells, even to eventually induce secondary fatty liver. On the contrary, repeated infusion of the sesame oil emulsion, of which the phospholipid was metabolized not only in the liver but also in the extrahepatic tissues and therefore assured more smooth utilization, did not cause any heavy burden on the liver, resulting in no abnormal accumulation of the phospholipid and no danger of the development of a fatty liver. Consequently, it is also understood from such metabolic process as above mentioned that the sesame oil emulsion has a remarkably better protein sparing effect and depot fat saving effect than the cod liver oil emulsion for the purpose of nutrition by intravenous infusion, as reported by Osa of our laboratory.

Viewed from the points of not only the adverse reaction reported by Otani but also the utilization in the body, in order to achieve the object of parenteral nutrition with fat by its intravenous administration in an emulsified form, a fatty substance, which contains glycerinesters of saturated higher fatty acids and such unsaturated fatty acids as oleic acid, linoleic acid, such as sesame oil, should be used and the use of fatty substance containing glycerinesters of lower fatty acids or highly unsaturated fatty acids should absolutely be avoided.

In starvation, the effective utilization of the infused fat will inevitably be lowered due to the induced shortage of various enzymes necessary for fat metabolism and glycogen. Recently, it has been clarified that various organic acids constituting the tricarboxylic acid cycle (T. C. A. cycle) have important significance as the "sparker" of fatty acid oxidation, and that the first reaction of fatty acid oxidation is provoked only by the oxidation of these organic acids. Acetyl coenzyme A (Acetyl CoA) which is formed by successive β-oxidation of fatty acid, is said to condense with oxaloacetic acid to enter into the T. C. A. cycle. Therefore, pantothenic acid, which is a chemical component of CoA, and glucose or glycogen, which yields oxaloacetic acid, play an important rôle in fat metabolism. Moreover, various enzymes, or more specifically various vitamins, are the indispensable elements for the smooth turn of the fatty acid cycle and T. C. A. cycle. Tsukada, Osa, Nishino and Hashino demonstrated that the simultaneous infusion of riboflavin was effective in the metabolism of the infused fat emulsion, and Hikasa and Ishigami pointed out that the infused fat was very smoothly disposed by the introduction of ascorbic acid. Hashino and Osa further pointed out the important rôle played by nicotinic acid infused simultaneously. Since various vitamins and glycogen as above mentioned become short in starvation, the turn of the fatty acid cycle and T. C. A.

cycle is checked and then the mechanism of fatty acid oxidation is very much detained, thus the phospholipid accumulates finally in the hepatic parenchymatous cells in large quantity. It was observed histochemically that in case of the infusion of the fat emulsion in these states, glucose and various vitamins such as riboflavin, ascorbic acid, nicotinic acid, pantothenic acid and vitamin B_1 etc. must be infused simultaneously with the fat emulsion. Since patients with malnutrition are the objects of our clinical application of parenteral nutrition with the fat emulsion, we ought to consider very seriously about the simultaneous infusion of the above mentioned drugs at all times.

V. CONCLUSION

1) In case of the intravenous administration of the fat emulsion prepared from glycerinesters of saturated higher fatty acids and unsaturated fatty acids such as oleic or linoleic acid, it is supposed that some part of the same is transported directly to fat depots.

2) However, the greater part of the infused fat globules is first phagocytized by the alveolar phagocytes, stellate cells and reticuloendothelial cells of the spleen; then the neutral fat is changed into phospholipid in these cells. Thereafter, the phospolipids, being changed from glycerinesters of highly unsaturated acids, enter chiefly into the hepatic parenchymatous cells, while the phospholipids, being changed from glycerinesters of saturated higher fatty acids and unsaturated higher fatty acids such as oleic or linoleic acid, enter not only into the hepatic parenchymatous cells but also into the extrahepatic tissues to be oxidized. Moreover, from the results obtained in the experiments on the oral administration of fat, it was found that phospholipids being changed from glycerinesters of lower fatty acids also enter into the hepatic parenchymatous cells only.

3) Since the phospholipid produced in the reticuloendothelial cells by the intravenous administration of the sesame oil emulsion is disposed not only in the liver but also in the extrahepatic tissues, repeated infusion of the same emulsion into the normal animals does not cause any accumulation of phospholipid in the hepatic parenchymatous cells. Therefore, in case of the intravenous infusion of fatty substance for the purpose of parenteral nutrition, the use of sesame oil emulsion is justifiably commendable.

4) Methionine accelerates not only the lipoidization of neutral fat but also the oxidation of fatty acid.

5) In case of starvation, even for the case of the sesame oil emulsion, it is preferable that glucose, riboflavin, niacin amide, ascorbic acid and pantothenic acid are infused simultaneously with the fat emulsion.

The author wishes to thank Dr. Yorinori Hikasa, lecturer of our clinic, for his great assistance and numerous valuable suggestions rendered throughout this investigation.

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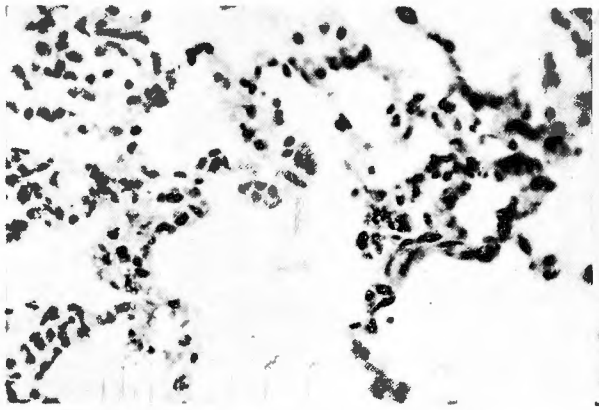

Fig. 1. Cat lung 10 minutes after infusion of sesame oil emulsion. Fat gloubules are phagocytized by numerous alveolar phagocytes. Oil red O stain, × 400.

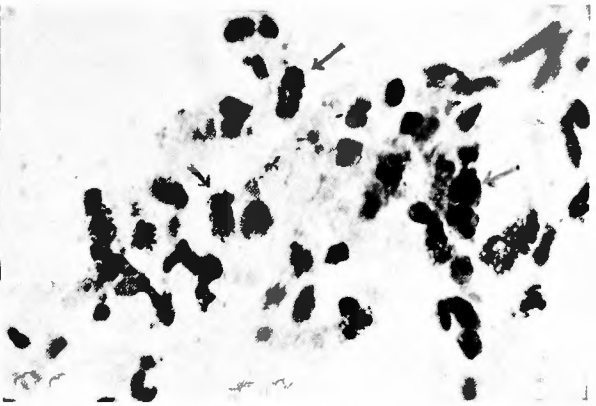

Fig. 2. Fat-filled alveolar phagocytes of the cat lung 30 minutes after infusion of sesame oil emulsion. Oil red O stain, × 900.

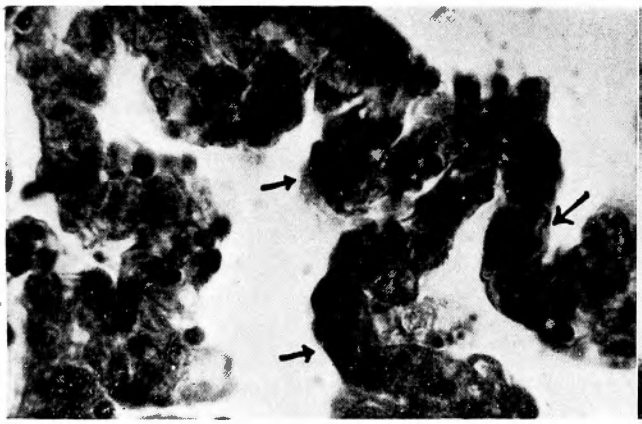

Fig. 3. Phospholipid in the alveolar phagocytes of the cat lung 30 minutes after infusion of sesame oil emulsion. SMITH-DIETRICH's stain, × 900.

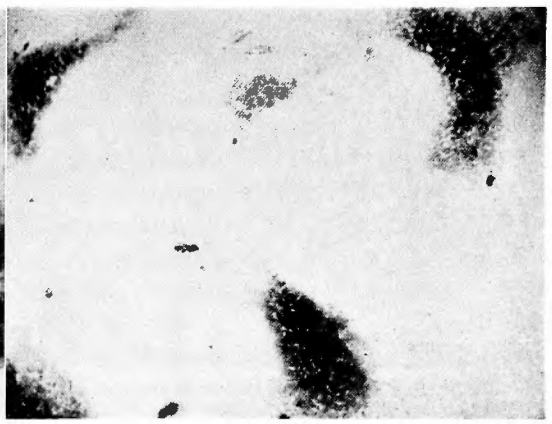

Fig. 4. Phospholipid appearing in small quantity in the cat liver 3 hours after infusion of sesame oil emulsion. SMITH-DIETRICH's stain, × 40.

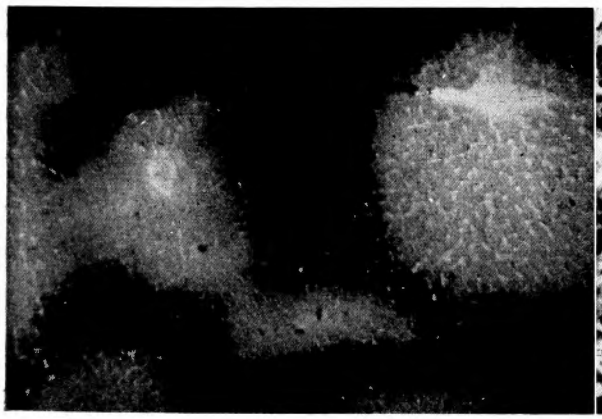

Fig. 5. Phospholipid appearing in large quantity in the cat liver 3 hours after infusion of cod liver oil emulsion. SMITH-DIETRICH's stain, × 40 (ASADA).

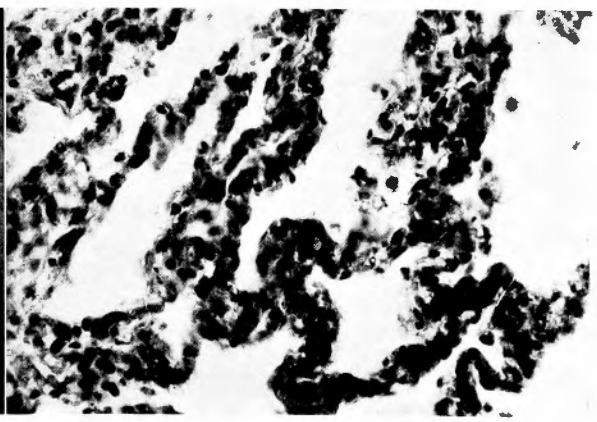

Fig. 6. Cat lung 30 minutes after infusion of triolein emulsion. Oil red O stain, × 400.

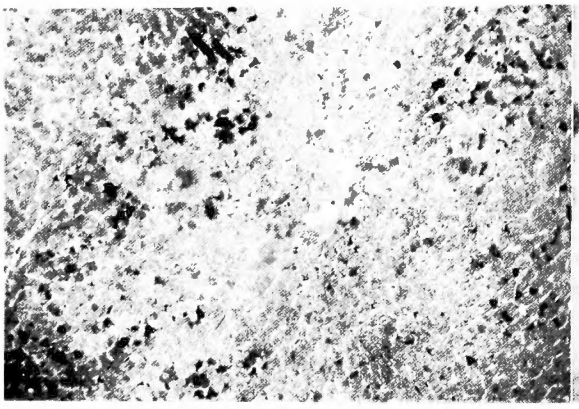

Fig. 7. Phospholipid appearing in very small quantity in the cat liver 3 hours after infusion of triolein emulsion. SMITH-DIETRICH's stain, ×80.

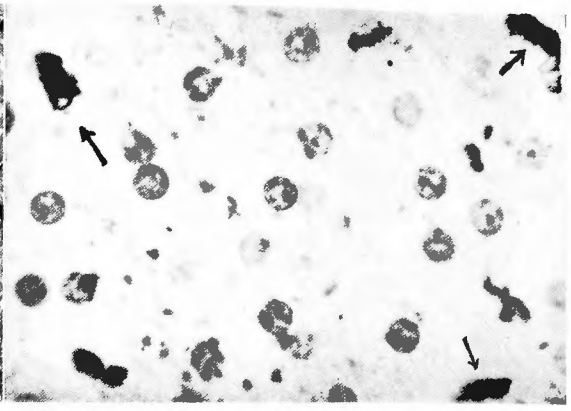

Fig. 8. Rabbit liver 30 minutes after infusion of sesame oil emulsion. Numerous stellate cells are filled with fat globules. Oil red O stain, ×900.

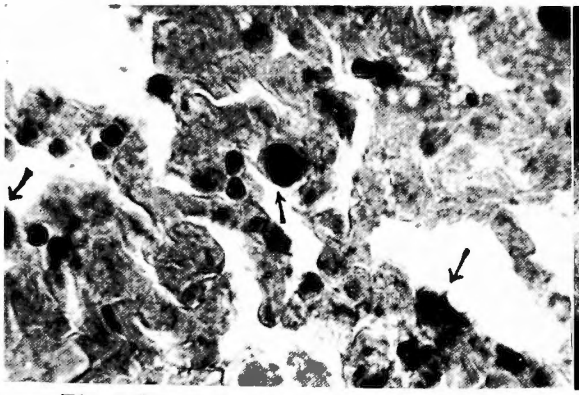

Fig. 9. Phospholipid in the alveolar phagocytes of the rabbit lung 30 minutes after infusion of methionine with sesame oil emulsion. SMITH-DIETRICH's stain, ×900.

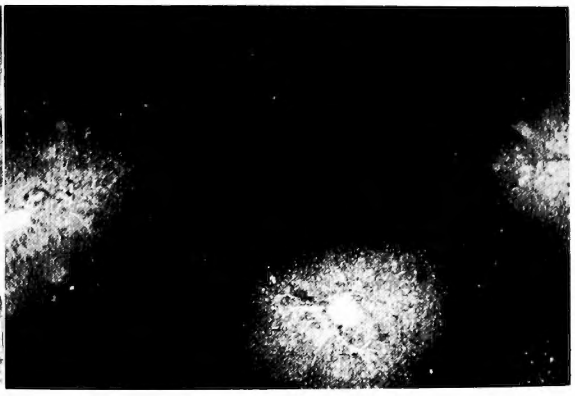

Fig. 10. Phospholipid appearing in large quantity in the liver 3 hours after infusion of sesame oil emulsion into starved rabbits. SMITH-DIETRICH's stain, ×40.

Fig. 11. Phospholipid appearing in small quantity in the liver 3 hours after simultaneous infusion of glucose and various vitamins with sesame oil emulsion into starved rabbits. SMITH-DIETRICH's stain, ×40.

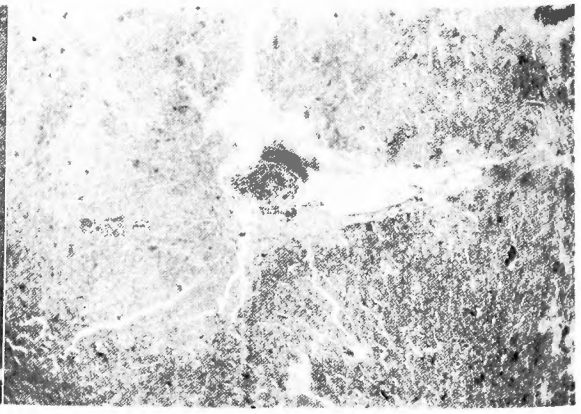

Fig. 12. Phospholipid in the rabbit liver after a 7 week infusion of sesame oil emulsion. SMITH-DIETRICH's stain, ×100.

Fig. 13. Rabbit liver after a 7 week infusion of sesame oil emulsion. Oil red O stain, ×100.

Fig. 14. Phospholipid appearing in large quantity in the cat liver 6 hours after oral administration of butter fat. SMITH-DIETRICH's stain, ×80.

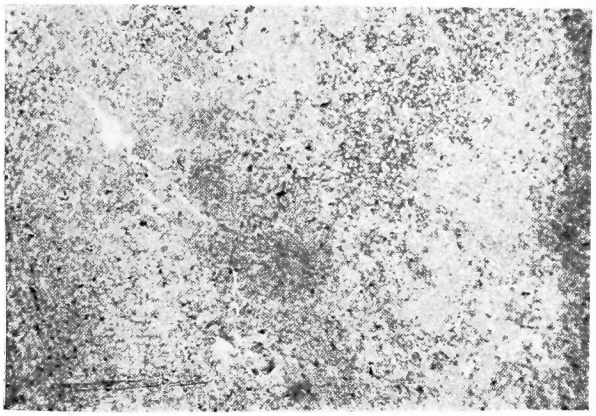

Fig. 15. Phospholipid appearing in small quantity in the cat liver 6 hours after oral administration of olive oil. SMITH-DIETRICH's stain, ×80.

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和文抄録

経静脈性脂肪輸入時の組織顕微化学的研究

(特に注入脂肪体の種類に基づく処理過程の差異について)

京都大学医学部外科学教室第2講座(指導：青柳安誠教授)
大学院学生　伊豆藏　健

教室創製の経静脈性輸入可能な各種の脂肪乳剤を試獣の静脈内に注入した場合，或は種々の脂肪を経口的に投与した場合に於ける脂質の生体内代謝過程を組織顕微化学的に追究し，且つその際の所見を比較検討して次の結論に達した．

(1) 静脈内に注入した脂肪球の大部分は，肺胞喰細胞，肝星細胞，脾臓の網内系細胞群に摂取され，ここで中性脂肪から phospholipid に変化する．併し，高級飽和脂肪酸並びにオレイン酸，リノール酸等の不飽和脂肪酸の glycerinester のみを含有する脂肪乳剤を注入した際は，その一部は貯臓脂肪に移行するものと思われる．

(2) 高度不飽和酸，或は低級脂肪酸の glycerinester から生じた phospholipid は，主として肝臓実質細胞に移行するが，高級飽和脂肪酸並びにオレイン酸，リノール酸等の不飽和脂肪酸の glycerinester から生じた phospholipid は肝臓実質細胞のみならず肝外組織にも移行する．

(3) ゴマ油乳剤注入時には，その phospholipid は肝臓のみならず肝外組織に於ても処理される故，これを健常試獣に連続反復注入しても，肝臓実質細胞内に phospholipid の蓄積を来す事もなく，脂肪肝の発生を見る事もない．故に非経口的栄養補給の目的で脂肪を直接静脈内に注入するに当つては，ゴマ油のような脂肪体を原料として使用すべきものと言い得る．

(4) メチオニンは中性脂肪の Phospholipid 化を促進すると共に，肝臓における脂肪酸の酸化をも促進する．

(5) 飢餓状態に際しては，たとえゴマ油乳剤を注入する場合でも，ブドウ糖並びにリボフラビン，ニコチン酸アミド，ビタミンC，パントテン酸及びビタミン B_1 等の各種のビタミン類の併用が必要である．